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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.
Targeting Hypertension in Patients with the Cardio-Renal Metabolic Syndrome

Edward Rojas, M.D.
Endocrine and Metabolic Diseases Research Center
University of Zulia
Venezuela
In 2025 it was predicted to increase by about 60% to a total of 1.56 billion (1.54–1.58 billion).

Prevalence of Hypertension in people aged 20 years or older by world region and sex in 2000 and 2025

“High blood pressure is a powerful, consistent, and independent risk factor for cardiovascular disease and renal disease”
Global projections for the number of people with diabetes (20-79 age group), 2007-2025 (millions)


Prevalence of Diabetic Kidney Disease in the US

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence</th>
<th>95% IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES III (1988-1998)</td>
<td>2.2%</td>
<td>1.8-2.6%</td>
</tr>
<tr>
<td>NHANES 1999-2004</td>
<td>2.8%</td>
<td>2.4-3.1%</td>
</tr>
<tr>
<td>NHANES 2005-2008</td>
<td>3.3%</td>
<td>2.8-3.7%</td>
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</table>

Trends

### CAUSAS DE MUERTE

<table>
<thead>
<tr>
<th></th>
<th>Mortalidad Diagnostica</th>
<th>Porcentajes (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Enfermedades del corazón (I05-I09, I11, I13, I21-I51)</td>
<td>24,977</td>
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<tr>
<td></td>
<td>Infarto agudo del miocardio (I21)</td>
<td>15,379</td>
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<tr>
<td></td>
<td>Enfermedad cardiaca hipertensiva (I11)</td>
<td>2,976</td>
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<tr>
<td></td>
<td>Enfermedad Isquémica crónica del corazón (I25)</td>
<td>2,653</td>
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<tr>
<td>2.</td>
<td>Cáncer (C00-C97)</td>
<td>18,343</td>
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<tr>
<td></td>
<td>Tumores malignos de los órganos digestivos. (C15-C26)</td>
<td>5,160</td>
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<tr>
<td></td>
<td>Tumores malignos de los órganos respiratorios e intratorácicos (C30-C39)</td>
<td>3,145</td>
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<tr>
<td></td>
<td>Tumores malignos de los órganos genitales femeninos. (C51-C58)</td>
<td>2,141</td>
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<tr>
<td>3.</td>
<td>Suicidios y Homicidios. (X60-Y09). (2)</td>
<td>9,748</td>
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<tr>
<td></td>
<td>Homicidios. (X85-Y09). (2)</td>
<td>8,805</td>
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<td></td>
<td>Suicidios. (X60-X84). (2)</td>
<td>943</td>
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<td>4.</td>
<td>Enfermedades Cerebrovasculares. (I60-I69)</td>
<td>9,391</td>
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<td></td>
<td>Hemorragia intracraneal (I61)</td>
<td>2,976</td>
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<tr>
<td></td>
<td>Otras enfermedades cerebrovasculares (I67)</td>
<td>2,173</td>
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<tr>
<td></td>
<td>Accidente vascular encefálico agudo, no especificado como hemorrágico o isquémico (I64)</td>
<td>1,576</td>
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<tr>
<td>5.</td>
<td>Accidentes de Todo Tipo. (V01-X59). (2)</td>
<td>9,353</td>
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<td></td>
<td>Accidentes de Trafico de Vehículos de Motor. (V01-V09). (2)</td>
<td>6,218</td>
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<tr>
<td></td>
<td>Otras Accidentes. (V50-X59). (2)</td>
<td>3,135</td>
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<tr>
<td>6.</td>
<td>Diabetes. (E10-E14)</td>
<td>7,181</td>
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<td>7.</td>
<td>Ciertas afecciones originadas en el período perinatal. (P06-P36) (3)</td>
<td>4,339</td>
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<td></td>
<td>Trastornos respiratorios y cardiovasculares específicos del período perinatal. (P20-P29) (3)</td>
<td>3,162</td>
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<tr>
<td></td>
<td>Infecciones específicas del período perinatal. (P35-P39). (3)</td>
<td>797</td>
</tr>
<tr>
<td></td>
<td>Feto y recién nacido afectado por factores maternos y por complicaciones del embarazo, del trabajo de parto y del parto (P00-P04) (3)</td>
<td>527</td>
</tr>
<tr>
<td>8.</td>
<td>Enfermedades crónicas de las vías respiratorias inferiores. (J40-J47)</td>
<td>3,225</td>
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<tr>
<td>9.</td>
<td>Influenza y neumonía. (J10-J18)</td>
<td>2,856</td>
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<tr>
<td></td>
<td>Neumonía. (J12-J18)</td>
<td>2,839</td>
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<tr>
<td></td>
<td>Influenza debida a virus no Identificado (J11)</td>
<td>17</td>
</tr>
<tr>
<td>10.</td>
<td>Enfermedades del hígado. (K70-K77)</td>
<td>2,483</td>
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<tr>
<td></td>
<td>Cirrosis y fibrosis Hepática. (K70.2, K70.3, K74)</td>
<td>1,769</td>
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<td></td>
<td>Enfermedad alcohólica del hígado (K70)</td>
<td>259</td>
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<td></td>
<td>Otras enfermedades del hígado (K76)</td>
<td>202</td>
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<tr>
<td>11.</td>
<td>Anomalías congénitas. (Q00-Q99)</td>
<td>2,212</td>
</tr>
<tr>
<td>12.</td>
<td>Enfermedad por virus de la inmunodeficiencia humana [VIH]. (B20-B24)</td>
<td>1,567</td>
</tr>
<tr>
<td>13.</td>
<td>Tumores benignos y de comportamiento incierto o desconocido. (D40-D48)</td>
<td>1,549</td>
</tr>
<tr>
<td>14.</td>
<td>Nefritis y Nefrosis. (N00-N19, N25-N29)</td>
<td>1,480</td>
</tr>
<tr>
<td></td>
<td>Insuficiencia renal crónica (N18)</td>
<td>1,071</td>
</tr>
<tr>
<td></td>
<td>Insuficiencia renal aguda (N17)</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>Insuficiencia renal no especificada (N19)</td>
<td>93</td>
</tr>
</tbody>
</table>
Cardiovascular Disease and all Cause Mortality are Increased in Men with Metabolic Syndrome

Lakka HM et al. JAMA 2002; 288:2709
Hypertension and Diabetes Mellitus
Pathophysiology
Obesity and Cardiovascular Risk

Dyslipidaemia
Total-C ↑
LDL-C ↑
Triglycerides ↑
Apo-B ↑
HDL-C ↓

Visceral Obesity

Endothelial dysfunction

Prothrombosis
Fibrinogen ↑
PAI-1 ↑

Inflammatory Response ↑ (TNFα, IL-1, IL-6)

ACE
AGT
RENIN
AT1R

Insulin resistance
Glucose intolerance
Hyperglycaemia
Type 2 diabetes

Renal
Hyperfiltration
Albuminuria

The Renin-Angiotensin System is Activated in Obese Women

Comparison of circulating renin-angiotensin-aldosterone system between 19 lean and 19 obese postmenopausal women.

Data given as mean±SD

*P<0.05

Activation of RAS is Reduced by Weight Loss

The circulating renin-angiotensin-aldosterone system before and after 5% weight loss in 17 obese post-menopausal women

Data given as mean±SD

*P<0.05

Relationship Between Reduction in Waist Circumference and Circulating Angiotensinogen

\[ r = 0.74, \quad r^2 = 0.54, \quad p = 0.0008 \]

Upregulation of ACE and AT$_1$R Genes In Isolated Subcutaneous Abdominal Adipocytes

Angiotensin II Inhibits Adipogenic Differentiation of Human Preadipocytes

Janke et al., Diabetes 2003
Ang II Inhibits Adipocyte Differentiation and Promotes Myocytic Lipid Deposition

Ang II Inhibits Adipocyte Differentiation and Promotes Myocytic Lipid Deposition

Ang II Inhibits Adipocyte Differentiation and Promotes Myocytic Lipid Deposition

- Ang I \rightarrow Ang II
- Ang II inhibits preadipocyte differentiation
- Ang II promotes myocytic lipid stores
- RAS-Blockade prevents excess lipids

small insulin-sensitive adipocytes

preadipocyte differentiation

myocytic lipid stores insulin sensitivity

Skeletal muscle phenotypic characteristics of patients with hypertension that predispose to insulin resistance

1. Altered composition of skeletal muscle tissue (less slow-twitch insulin-sensitive muscle fibers and increased fat interspersed between skeletal muscle fibers).

2. Decreased blood flow and delivery of insulin and glucose to skeletal muscle tissue due to vascular hypertrophy and vasoconstriction.

3. Postreceptor abnormalities in metabolic signaling responses to insulin in skeletal muscle tissue.
Skeletal Muscle Cell

Angiotensin II

RhoA

NADP-H Oxidase

Rac-GTP

O2-

+NOS

Arg

GLUT-4 Vesicle

Akt

PI3k

PIP-3

PIP-2

ONOO-

Hypertension and Diabetes Mellitus

Therapeutics
Facts:

“Hypertensive patients who were taking B-blockers had a 28% higher risk of development of diabetes compared with those taking no antihypertensive medications”

“Potential mechanisms by which B-blockers may increase insulin resistance include weight gain and decreased blood flow to skeletal muscle tissues”

New Onset Diabetes Mellitus and Antihypertensive Therapy

RAS Blockade Increases Adiponectin In Hypertensive Patients

*\( p < 0.05 \)

Before Temocapril (4 mg/d)  
After  

Before Candesartan (8 mg/d)  
After  

2-week treatment period

Effect of RAS Blockade On Fasting Insulin in Hypertensives

Masato Furuhashi et al. Blockade of the Renin-Angiotensin System Increases Adiponectin Concentrations. in Patients With Essential Hypertension. Hypertension 2003, 42:76-81:
Effects of Simvastatin, Losartan, and Combined Therapy on Adiponectin Levels in Hypercholesterolemic, Hypertensive Patients (n=47)

Effects of Simvastatin, Combined Therapy, and Losartan on Insulin Sensitivity in Hypercholesterolemic, Hypertensive Patients (n=47)

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>RAMIPRIL GROUP (N=4645)</th>
<th>PLACEBO GROUP (N=4652)</th>
<th>RELATIVE RISK (95% CI)*</th>
<th>z STATISTIC</th>
<th>P VALUE †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>742 (16.0)</td>
<td>852 (18.3)</td>
<td>0.85 (0.77–0.94)</td>
<td>-3.17</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>554 (11.9)</td>
<td>565 (12.1)</td>
<td>0.98 (0.87–1.10)</td>
<td>-0.41</td>
<td>0.68</td>
</tr>
<tr>
<td>Complications related to diabetes§¶</td>
<td>299 (6.4)</td>
<td>354 (7.6)</td>
<td>0.84 (0.72–0.98)</td>
<td>-2.16</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>141 (3.0)</td>
<td>160 (3.4)</td>
<td>0.88 (0.70–1.10)</td>
<td>-1.16</td>
<td>0.25</td>
</tr>
<tr>
<td>Other outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure‡</td>
<td>417 (9.0)</td>
<td>535 (11.5)</td>
<td>0.77 (0.67–0.87)</td>
<td>-4.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>37 (0.8)</td>
<td>59 (1.3)</td>
<td>0.62 (0.41–0.94)</td>
<td>-2.28</td>
<td>0.02</td>
</tr>
<tr>
<td>Worsening angina§</td>
<td>1107 (23.8)</td>
<td>1220 (26.2)</td>
<td>0.89 (0.83–0.96)</td>
<td>-2.91</td>
<td>0.004</td>
</tr>
<tr>
<td>New diagnosis of diabetes¶</td>
<td>102 (3.6)</td>
<td>155 (5.4)</td>
<td>0.66 (0.51–0.85)</td>
<td>-3.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unstable angina with electrocardiographic changes‡</td>
<td>175 (3.8)</td>
<td>180 (3.9)</td>
<td>0.97 (0.79–1.19)</td>
<td>-0.30</td>
<td>0.76</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
† P values were calculated with use of the log-rank test.
‡ These events were centrally adjudicated.
§ All cases are included, whether or not hospitalization was required.
¶ Complications related to diabetes include diabetic nephropathy (defined as urinary albumin excretion of at least 300 mg per day or urinary protein excretion of 500 mg per day), the need for renal dialysis, and the need for laser therapy for diabetic retinopathy.
‖ The denominator in the ramipril group is the 2837 patients who did not have diabetes at base line. The denominator in the placebo group is the 2883 patients who did not have diabetes at base line.
“ACE inhibitors should be considered for the initial treatment of hypertension, following appropriate reproductive counseling due to its potential teratogenic Effects”
Conclusions

1. Diabetes and hypertension prevalence are expected to increase worldwide.

2. Coexistence of diabetes and hypertension in the same patient is greater than chance alone would predict.

3. Local adipose tissue RAAS plays an important role in systemic Hypertension and insulin resistance.

4. Ang II is able to block adipocyte differentiation through ATR1 and cause ectopic fat accumulation in liver and muscle.

5. ACEI’s and ARB’s should be considered in hypertensive patients who have diabetes or obesity.

6. Nonetheless, lifestyle changes have demonstrated the best results.
Targeting Hypertension in Patients with Cardiorenal Metabolic Syndrome

Edward Rojas · Manuel Velasco · Valmore Bermúdez · Zafar Israili · Peter Bolli

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E. Rojas (✉) · V. Bermúdez
Endocrine and Metabolic Diseases Research Centre “Dr. Felix Gomez”, University of Zulia, 20th Avenue, Maracaibo 4004, Venezuela
e-mail: rojas_187@hotmail.com

M. Velasco
Clinical Pharmacology Unit of José María Vargas School of Medicine, Central University of Venezuela, Caracas, Venezuela

Z. Israili
Emory University School of Medicine, Atlanta, GA, USA

P. Bolli
Clinical Professor of Medicine, McMaster University Hamilton, Hamilton, ON, Canada

Published online: 31 July 2012
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